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## Variants for HDL-C, LDL-C and Triglycerides Identified from Admixture Mapping and Fine-Mapping Analysis in African-American Families

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### Abstract

**Background**—Admixture mapping of lipids was followed-up by family-based association analysis to identify variants for cardiovascular disease in African-Americans.

**Methods and Results**—The present study conducted admixture mapping analysis for total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides. The analysis was performed in 1,905 unrelated African-American subjects from the National Heart, Lung and Blood Institute's Family Blood Pressure Program. Regions showing admixture evidence were followed-up with family-based association analysis in

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3,556 African-American subjects from the FBPP. The admixture mapping and family-based association analyses were adjusted for age, age<sup>2</sup>, sex, body-mass-index, and genome-wide mean ancestry to minimize the confounding due to population stratification. Regions that were suggestive of local ancestry association evidence were found on chromosomes 7 (LDL-C), 8 (HDL-C), 14 (triglycerides) and 19 (total cholesterol and triglycerides). In the fine-mapping analysis, 52,939 SNPs were tested and 11 SNPs (8 independent SNPs) showed nominal significant association with HDL-C (2 SNPs), LDL-C (4 SNPs) and triglycerides (5 SNPs). The family data was used in the fine-mapping to identify SNPs that showed novel associations with lipids and regions including genes with known associations for cardiovascular disease.

**Conclusions**—This study identified regions on chromosomes 7, 8, 14 and 19 and 11 SNPs from the fine-mapping analysis that were associated with HDL-C, LDL-C and triglycerides for further studies of cardiovascular disease in African-Americans.

### Keywords

lipids; genetics; association studies; African-Americans; admixture mapping analysis

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### Background

Inadequate control of lipids is a key indicator of poor cardiovascular health, which is a substantial public health issue worldwide. Approximately 2.6 million deaths worldwide annually are due to poorly-controlled cholesterol<sup>1</sup>. Variability in lipids is affected by genetic and environmental factors, and the heritability of key lipids has been estimated to range between 58% and 69% for HDL-C, LDL-C and triglycerides, based on studies from the Framingham Heart Study Offspring cohort<sup>2</sup>.

Several genome-wide association studies (GWAS) have successfully identified genetic variants that are associated with lipid traits<sup>2-10</sup>. Recently, two association analyses using GWAS data suggested that a number of SNPs associated with lipids in European ancestry populations may have effects in the same direction across different populations, including those of African and Hispanic ancestry<sup>5, 11</sup>. The empirical results, combined with those authors' reports of allelic heterogeneity and population-specific variants for lipids, emphasize the importance of conducting genetic studies in diverse study populations to identify variants.

Admixture mapping is a tool that may be used to discover these variants by utilizing the disparities in disease prevalence between ancestral populations of admixed populations to identify genomic regions and genetic variants that are associated with a phenotype<sup>12, 13</sup>. In these analyses, the frequency of a risk allele is expected to vary between ancestral populations of an admixed study population. It is assumed that, in a recently admixed population, affected subjects have increased ancestry for the population that has a greater frequency of the risk allele at the causal variant, compared to controls. Ancestry at the causal variant is also expected to be greater than the average genome-wide ancestry. This increased ancestry has been previously reported in hypertension cases<sup>14</sup>. In African-Americans, some genomic regions have been identified previously for lipids using admixture mapping, including 8q11-8q21 for HDL-C<sup>5, 15</sup>.

In the current study, admixture mapping analyses were conducted to identify genomic regions associated with lipid traits: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). The regions showing association evidence with local ancestry were followed up by fine-mapping association analysis using SNPs in families.

## Methods

### Sample

The study samples were obtained from the NHLBI's Family-Based Blood Pressure Program (FBPP). The FBPP consists of 4 Networks: GenNet, GENOA, HyperGEN, and SAPPHiRE. Each Network is a multi-center study that focuses on the genetic causes of hypertension and associated traits in African Americans, Asians and Asian Americans, European Americans, and Mexican Americans<sup>16</sup>. The FBPP study design was set up for linkage analysis, and the 4 networks in the FBPP ascertained families through probands with increased blood pressure or hypertension.

The current study was conducted in African Americans who were recruited from three FBPP Networks: The Hypertension Genetic Epidemiology Network (HyperGEN) in Birmingham, Alabama and Forsyth County, North Carolina; the Genetic Epidemiology Network of Atherosclerosis (GENOA) in Jackson, Mississippi; and the GenNet study in Maywood, Illinois. Further details of the FBPP Networks are available elsewhere<sup>16</sup>. The current study was approved by the University Hospitals Case Medical Center institutional review committee.

The admixture mapping analysis was conducted in 1,905 unrelated subjects that were selected from the overall FBPP data as described previously<sup>17</sup>. Briefly, the normotensive control was selected first from the families, if available. If multiple controls were available, the oldest control was chosen. In the cases, the youngest hypertensive case in the family was selected. Subjects with age < 19 years or age > 80 years or average global African ancestry < 2.5% were removed from the dataset.

For the fine-mapping study, chromosomal regions that showed local ancestry association evidence for the phenotypes were selected for follow-up analysis. There were 3,556 subjects with complete phenotype and genotype information in 1,459 pedigrees from the FBPP in the fine-mapping analysis.

### Genotyping

The FBPP networks obtained blood samples from the study participants and DNA was extracted by standard methods. 2,593 evenly spaced ancestry-informative markers (AIMs) were identified across the genome that maximized the difference in allele frequency for the ancestral populations, HapMap CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) and HapMap YRI (Yoruba in Ibadan, Nigeria). These SNPs were selected from those that were available on the Illumina Human 1M, Illumina 650K, and Affymetrix 6.0 arrays. These AIMs were genotyped for the 1,905 unrelated subjects using the Illumina iSelect Custom Bead Chip at the University of California San

Francisco<sup>15, 17-20</sup>. After dropping SNPs with call rate  $< 0.95$  and Illumina GenTrain score  $< 0.7$ , a final dataset of 2,507 AIMs in 1,905 unrelated subjects was used in the admixture mapping analysis.

Two of the four FBPP Networks had GWAS data. The subjects from the GENOA network were genotyped using the Affymetrix Array 6.0 and Illumina 1M arrays, and SNPs were imputed to obtain a complete dataset (imputation  $R^2 > 0.5$ ). The subjects from the HyperGEN network were genotyped using the Affymetrix Array 6.0 and the Affymetrix Array 5.0, and imputation was performed for a complete dataset (imputation  $R^2 > 0.3$ ). Quality control measures were performed separately for the GENOA and HyperGEN samples. SNPs with call rates less than 95% were excluded<sup>21</sup>. There were an additional 872 African-American subjects from the HyperGEN and GENOA networks who were not genotyped with conventional GWAS platforms; these individuals were genotyped using the Affymetrix Axiom Genome-Wide 1 array. SNPs were called using the Affymetrix Genotyping Console (GTC) by analyzing CEL files of intensity calculations from the Affymetrix Axiom Genome-Wide 1 arrays ([www.affymetrix.com](http://www.affymetrix.com)). SNPs with call rates  $< 95\%$  were excluded. The three datasets were combined in the fine mapping analysis, and the total sample size was 3,556 subjects with complete information. The combined genotyping data were examined for Mendelian errors and departures from Hardy-Weinberg Equilibrium ( $p < 0.001$ ), and 30 SNPs on chromosome 19 were removed. This analysis also helped to reduce the effect of using different genotyping arrays. After all of the quality control measures, 52,939 SNPs were analyzed in five regions identified from the admixture mapping analysis.

### Statistical Analyses

Two software programs, ADMIXPROGRAM and SABER, were used for estimating an individual's local ancestry<sup>22, 23</sup>. Both programs use maximum likelihood methods to estimate locus-specific ancestry, using SNPs as AIMs<sup>13</sup>. ADMIXPROGRAM uses a Hidden Markov Model to estimate the ancestry at each locus, where conditional on a hidden state, the genotype depends on its ancestral allele frequency, assuming that AIMs are in linkage equilibrium in the ancestral populations<sup>13, 24</sup>. It also utilizes a continuous gene-flow model to model the chromosome crossovers between ancestral populations, and this model is applicable to admixed populations with two ancestral populations, such as African-Americans<sup>13, 22</sup>. SABER uses a Markov-Hidden Markov Model for local ancestry estimation, and this model uses densely-spaced AIMs, such as those from a GWAS, to account for pair-wise LD in the ancestral populations<sup>13, 24</sup>. In addition, SABER models the local ancestry probability with a transition matrix using an intermixing model that accounts for more than two ancestral populations with separate admixing times, such as Hispanic populations<sup>13, 23</sup>.

The performance of the software was compared and the admixture mapping results were similar. As the population of interest had two ancestral populations, the estimates from ADMIXPROGRAM were used. The regions showing local ancestry association evidence with the estimates from ADMIXPROGRAM were followed up with fine-mapping association analysis.

Linear regression analysis was performed similarly to previous admixture mapping studies<sup>20, 25</sup>. Specifically, let  $y_i$  be the trait value of individual  $i$ . Let  $A_{ij}$  be the African  $j^{\text{th}}$  ancestry at the AIM and  $\bar{A}_i$  be the average African Ancestry of individual  $i$ .  $A_{ij}$  was estimated by ADMIXPROGRAM and  $\bar{A}_i$  was calculated as the mean of  $A_{ij}$  for all AIMS. The linear regression analysis was performed as

$y_i = \beta_0 + \beta_1 \bar{A}_i + \beta_2 (A_{ij} - \bar{A}_i) + \beta_3 SEX + \beta_4 AGE + \beta_5 AGE^2 + \beta_6 BMI + \varepsilon_i$  and tested the null hypothesis  $\beta_2 = 0$ , which was used to assess statistical significance in admixture mapping. To test the null hypothesis,  $\beta_2 = 0$ , a p-value  $< 0.001$  was considered as suggestive evidence of association in admixture mapping analysis. This p-value was chosen to compromise between the power of admixture mapping and of follow-up association analysis, that is, to retain an adequate number of genomic regions in admixture mapping analysis while reducing the number of SNP tests performed in the association analysis<sup>20, 26</sup>. A region of admixture mapping was defined as comprising the markers that were within the 1 unit drop of  $-\log_{10}(\text{p-value})$  from the peak signal on either side. Average African ancestry  $\bar{A}_i$  was included in the regression model to adjust for population stratification.

In the fine-mapping analysis, family-based association analysis using the ASSOC program in S.A.G.E. software v. 6.3.0 was performed. ASSOC was selected for this analysis because it can easily incorporate covariates, and it is more powerful than the transmission disequilibrium test. ASSOC is a linear regression model incorporating familial correlation among members within a pedigree through a mixed model, which is similar to GWAF<sup>27</sup>. Briefly, ASSOC applies a linear mixed model:  $y = \beta_0 + \beta_1 g + \varepsilon$ , where  $y$  is the residual after adjusting for covariates,  $\varepsilon \sim MVN(0, V)$  and  $V$  is a variance-covariance matrix. For members between families, the correlation is 0. For members within the same family, the correlation is twice of the kinship coefficient. The maximum likelihood method is used to estimate the parameters. Residuals were calculated for each trait after adjusting for the covariates (age, age<sup>2</sup>, sex, BMI and 10 PCs). For each trait, we did not observe substantial departure from a normal distribution. The SNP-specific heritability was calculated by the formula  $4\beta^2 p(1 - p) / \text{total trait variance}$ , where  $\beta$  is the estimated beta and  $p$  is the allele frequency of the effect allele.

For the family samples, the first ten principal components were estimated to account for population stratification as described elsewhere<sup>28</sup>. Briefly, the PCs for all founders were calculated and the PCs of the non-founders were projected according to their genotype data<sup>28</sup>. Principal component (PC) analysis was conducted using FamCC v.1.0 software. The PCs of founders and non-founders were similar to the PCs that were calculated from founders only.

The analyses in this study were conducted with PLINK software, SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA), Stata 9.2 (StataCorp. 2005. *Stata Statistical Software: Release 9*. College Station, TX: StataCorp LP), and FamCC v.1.0 software<sup>29</sup>. Additional information was obtained from the Database of Single Nucleotide Polymorphisms (dbSNP), the UCSC Genome Browser database, and the SNP Annotation and Proxy Search (SNAP) tool<sup>30-32</sup>.

## Results

### Admixture Mapping

Admixture mapping analyses were conducted genome-wide for total cholesterol, HDL-C, LDL-C and triglycerides in a sample of 1,905 unrelated African-American subjects in the FBPP. The descriptive statistics were presented in Table 1. The admixture mapping analyses for total cholesterol, HDL-C, LDL-C and triglycerides were presented in Supplemental Figures 1a-1d.

In the admixture mapping analysis, chromosomal regions suggesting evidence of local ancestry association were those with  $p$ -value  $< 0.001$  ( $-\log_{10}(p\text{-value}) \geq 3$ ). The results for each phenotype were reported with the associated peak, corresponding SNP,  $-\log_{10}(p\text{-value})$  of the SNP, and region of admixture mapping (Table 2).

For total cholesterol, local ancestry association evidence was suggested on chromosome 19 (4.9–40.1 Mega base pairs (Mb)). The maximum  $-\log_{10}(p\text{-value})$  in this region was at SNP rs901792 (19p13,  $-\log_{10}(p\text{-value}) = 3.06$ ) in *TRIC-A* (*TMEM38A*). For HDL-C, suggested ancestry evidence was found on chromosome 8 (16.8-27.4 Mb) and the peak was at SNP rs13438843 (8p21,  $-\log_{10}(p\text{-value}) = 3.05$ ). For LDL-C, ancestry evidence was suggested on chromosome 7 (16.8-23.9 Mb), and the peak SNP in this region was at rs7793253 (7p15,  $-\log_{10}(p\text{-value}) = 3.21$ ). For triglycerides, ancestry association evidence was suggested on chromosome 14 (78.3- 95.6 Mb) with the maximum  $-\log_{10}(p\text{-value})$  at rs3825663 (14q32,  $-\log_{10}(p\text{-value}) = 3.26$ ) in *TDPI*. Admixture evidence was also suggested for triglycerides on chromosome 19 (1.6- 8.1 Mb) with the peak at rs8110664 (19p13,  $-\log_{10}(p\text{-value}) = 3.96$ ). These regions on chromosomes 7, 8, 14 and 19 were selected for the fine-mapping association analysis.

### Fine-Mapping Analysis

For each trait, only the chromosomal regions showing local ancestry association evidence in the admixture mapping analysis were studied in the family-based association analysis. The association models were adjusted for age, age<sup>2</sup>, sex, BMI and the first ten PCs. A summary of the significant fine-mapping results was reported in Table 3.

Overall, 52,939 SNPs were tested in the fine-mapping analysis, and the number of SNPs tested for each phenotype was: total cholesterol (17,258 SNPs), HDL-C (10,995 SNPs), LDL-C (6,964 SNPs) and triglycerides (15,328 SNPs on chromosome 14 and 2,394 SNPs on chromosome 19). Quantile-quantile plots (Figures 1a-1e) presented the observed and expected  $-\log_{10}(p\text{-value})$  from the fine-mapping analyses. These plots showed substantial deviation from the diagonal line after accounting for population stratification for HDL-C, LDL-C and triglycerides (chromosome 14), suggesting that there were true variants associated with these traits in these regions. Genomic inflation factors ( $\lambda$ ) were calculated for each plot as described previously and noted below the quantile-quantile plots<sup>33</sup>. Genomic inflation factors  $> 1.00$  usually indicated that population stratification was not well-controlled. However, as these regions suggested association evidence in the admixture mapping, the observed inflated genomic factors were reasonable and can be attributed to the linkage disequilibrium among the SNPs and true associated variants in these regions.

For HDL-C, two SNPs were significant after testing 10,995 SNPs. The most significant SNP, rs10096633 ( $p = 4.17 \times 10^{-7}$ ; 8p21) was not in any known genes, but it was near *LPL* (lipoprotein lipase). The second SNP rs13702 ( $p = 3.44 \times 10^{-6}$ ; 8p21) was located within *LPL*. These results were consistent with the well-established association between *LPL* and HDL-C<sup>3, 9</sup>.

For LDL-C, 4 SNPs were significant after testing 6,964 SNPs. The most significant SNP was rs12534314 ( $p = 9.29 \times 10^{-6}$ ; 7p15), which was in high LD ( $D' = 1.00$ ,  $r^2 = 1.00$ ) with rs12531660 ( $p = 2.13 \times 10^{-5}$ ; 7p15). SNPs rs12534314 and rs6966083 ( $p = 1.02 \times 10^{-5}$ ; 7p21) were not located within genes, but SNP rs10486301 ( $p = 9.37 \times 10^{-5}$ ; 7p21) was located within *HDAC9*.

On chromosome 14, there were 15,328 SNPs tested for triglycerides in the fine-mapping analysis, and five of these SNPs were significant. Three of the five SNPs were in high LD ( $D' = 1.00$ ,  $r^2 = 1.00$ ), resulting in three independent SNPs for triglycerides. The most significant SNP was rs10483943 (14q31) ( $p = 3.35 \times 10^{-7}$ ), which was not in any known gene. SNPs rs759512 ( $p = 7.74 \times 10^{-7}$ ) and rs757645 ( $p = 1.92 \times 10^{-6}$ ) were in close proximity to rs10483943. In addition, SNPs rs10130530 (14q24) in *NRXN3* and rs11620666 (14q32) in *TTC7B* were significantly associated with triglycerides ( $p = 2.13 \times 10^{-6}$  and  $p = 3.35 \times 10^{-7}$ , respectively).

Graphs were created to summarize the results from the admixture mapping, family-based fine-mapping analysis, and large GWAS in the literature (Figures 2a-2e). The SNP results from the fine-mapping analysis and the SNP results from literature were overlaid on the admixture mapping results from the present study.

An *in silico* replication of the lipid results was performed using data from the NHLBI's Candidate Gene Association Resource (CARE) Consortium. The CARE Consortium is a multi-site, multi-ethnic study comprised of nine cohort studies, including five African-American cohorts, that examines genetic variation in lipids, blood pressure and many other traits<sup>34, 35</sup>. In lipid analysis, the residuals of both HDL-C and LDL-C were standardized, resulting smaller estimated genetic effect sizes than the current study. However the different transformations did not affect replication result. For HDL-C ( $N = 7,813$ ), SNPs rs10096633 ( $p = 1.48 \times 10^{-9}$ ) and rs13702 ( $p = 2.49 \times 10^{-9}$ ) were significantly associated with the phenotype (Table 3). These results had the same direction of effect as the FBPP results, and the p-values were more significant in the CARE results.

For LDL-C ( $N = 7,565$ ), only rs6966083 ( $p = 0.01181$ ) was significantly associated with the trait, while rs12534314 ( $p = 0.9183$ ) and rs10486301 ( $p = 0.8083$ ) were not. Only the result for rs10486301 was in the same direction for both FBPP and CARE. In addition, the p-values were more significant for LDL-C in the FBPP results.

## Discussion

Admixture mapping analysis of lipid traits was conducted for unrelated African-Americans in the FBPP, and the chromosomes that contained regions of admixture evidence were followed-up with fine-mapping association analysis using family data. This procedure has



been suggested to identify SNP associations which may be missed by traditional GWAS<sup>20, 26</sup>. The admixture mapping analysis capitalized on the recent admixture of African-American population to narrow down regions of interest for a trait, and the family-based analysis allowed for fine mapping of the regions.

Five regions in the admixture mapping analysis that showed local ancestry evidence were reported for association with lipids. In the fine-mapping analysis, 11 SNPs (8 independent SNPs) were associated with lipid traits. Findings for four SNPs were consistent with previously reported results and the other four were novel associations.

Significant admixture associations were reported for total cholesterol, and triglycerides on chromosome 19, but significant fine-mapping results were not found in these regions. For total cholesterol, the reported admixture region included 4 SNPs that were previously reported for total cholesterol, HDL-C and LDL-C in a large GWAS of blood lipids in populations of European ancestry populations<sup>6</sup>.

For HDL-C, the most significant SNP from the fine-mapping, rs10096633 was near *LPL* (lipoprotein lipase) and the second SNP rs13702 was located within *LPL*. This gene has a key role in the hydrolysis of the triglyceride component of a number of lipoproteins and lipid metabolism<sup>36-38</sup>. The relationship between *LPL* and HDL-C has been well-established, and a number of studies have identified common variants in *LPL* that are associated with reduced HDL-C (Ser447stop, Asn291Ser, and D9N)<sup>39-41</sup>. Recent studies have also identified *LPL* variants in diverse populations and have reported associations between rare *LPL* variants and reduced response to fenofibric acid treatment for low HDL-C<sup>5, 42, 43</sup>.

For LDL-C, the admixture region on chromosome 7 included rs12670798 (*DNAH11*), which was previously reported for association with LDL-C and total cholesterol<sup>6</sup>. The most significant SNP in the fine-mapping analysis, SNP rs12534314, was for LDL-C and was located near *STEAP1B*. Although not directly associated with a lipid phenotype, the region around *STEAP1B* was previously reported for association with all-cause death on dialysis in African-Americans with type 2 diabetes<sup>44</sup>. SNP rs10486301 in *HDAC9* was reported for association with stroke and obesity phenotypes<sup>45, 46</sup>.

For triglycerides, the admixture peak on chromosome 14 was located at rs3825663 in *TDP1*, which was reported for association with carotid plaque in a Dominican family study<sup>47</sup>. In the fine-mapping, SNP rs10130530 in *NRXN3* was previously reported for association with obesity, body-mass-index, and waist circumference in GWAS<sup>48-50</sup>. SNP rs11620666 in *TTC7B* was reported in a GWAS of European-ancestry individuals for cytomegalovirus (CMV) antibody response, and CMV was found to be associated with atherosclerosis and acute coronary events<sup>51-53</sup>. The admixture regions for triglycerides included SNPs that were not previously reported for association in the lipids GWAS<sup>6</sup>.

Finally, the results from the admixture mapping analysis, the fine-mapping association analysis, and results from GWAS were evaluated concurrently (Figures 2a-2e)<sup>3-9, 43, 54-57</sup>. As expected, the fine-mapping SNPs for HDL-C, LDL-C and triglycerides (chromosome 14) were quite consistent with the admixture results with regards to the location of the peak SNPs. Yet, it seemed that the precision and magnitude of the SNP results benefitted from the

testing of dense SNPs in the family-based, fine-mapping analysis. For example, for LDL-C, the locations of the most significant SNPs were consistent with the peaks from the admixture analysis; however, the magnitude of the p-values indicate that the strength of evidence showing departure from the null hypothesis (of no association) was stronger in the fine-mapping analysis than in the admixture mapping analysis. Consequently, the admixture mapping results were narrowed down to the significant SNPs from the fine-mapping analysis. Further, these graphs demonstrated consistencies between the studies, despite being performed in different populations, which was also reported in recent studies<sup>5, 21</sup>. The graphs also showed that the current study's use of African-American subjects revealed novel findings that were not found in studies of other populations.

By conducting a two-stage analysis, this study reduced the number of SNPs tested in the family-based association study by focusing on variants in candidate regions. This method of analysis has the potential to uncover the variants missed by traditional studies, such as GWAS<sup>20,26</sup>.

In summary, the current study reports five chromosomal regions that showed association of local ancestry evidence with cardiovascular phenotypes. In the follow-up fine-mapping analysis in families, 8 independent SNPs were associated with lipid traits. These regions and SNPs may aid in identifying potential therapeutic targets for cardiovascular disease traits. Furthermore, these regions are candidates for future sequencing studies and further lipid studies, especially in African-American populations. The present study also suggested the benefits of multi-stage analysis methods for genetic studies, particularly in recently admixed populations that were not well-studied with traditional association studies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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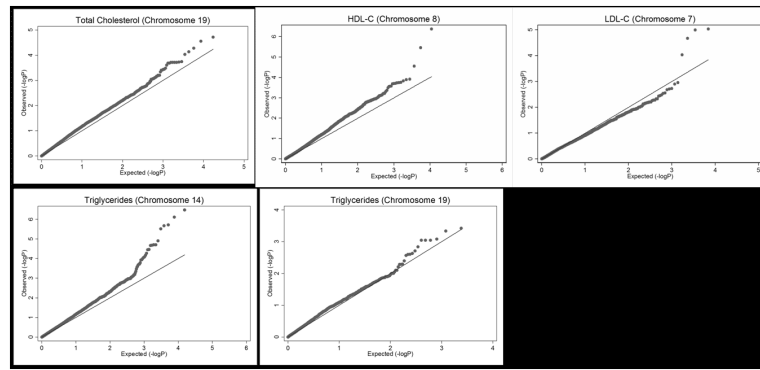
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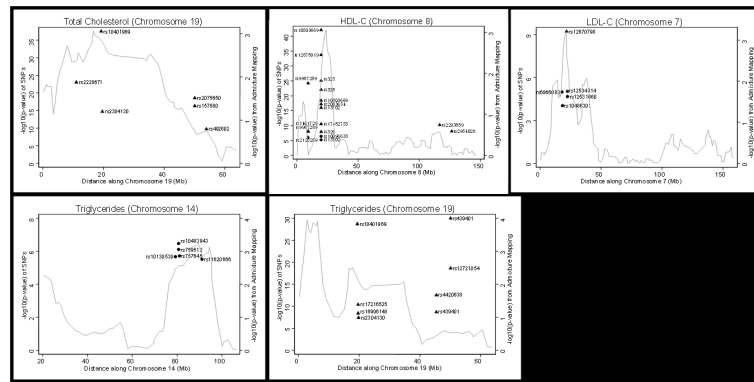
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**Figures 1.**

Quantile-Quantile Plots of Fine-Mapping Analysis in Families. 52,939 SNPs were tested, and the number of SNPs tested for each phenotype was: total cholesterol (17,258 SNPs), HDL-C (10,995 SNPs), LDL-C (6,964 SNPs) and triglycerides (15,328 SNPs on chromosome 14 and 2,394 SNPs on chromosome 19). Significant results were reported for HDL-C, LDL-C and triglycerides (chromosome 14). **A.** Total cholesterol, **B.** HDL-C, **C.** LDL-C, **D.** Triglycerides on chromosome 14, **E.** Triglycerides on chromosome 19



**Figure 2.** Combined Analyses Plots. The SNP results from the fine-mapping analysis and from the literature were overlaid on the admixture mapping results from the present study. Results from the present study were represented by circles, and results from the literature were represented by triangles. Additional significant results were reported by Teslovich et al. for LDL-C at rs12670798 (21.6 Mb) and rs2072183 (44.5 Mb) on chromosome 7 and for total cholesterol at rs6511720 (11.1 Mb) and rs4420638 (50.1 Mb) on chromosome 19 without p-values. **A.** Total cholesterol, **B.** HDL-C, **C.** LDL-C, **D.** Triglycerides on chromosome 14, **E.** Triglycerides on chromosome 19



**Table 1**

## Summary Statistics

Variable	N	Mean	Median	Min, Max
Mean African Ancestry	1905	83.7%	85.5%	33.5%, 98.8%
Age (years)	1905	48.8	49.0	19.0, 80.0
BMI kg/m <sup>2</sup>	1905	31.1	29.9	13.8, 70.7
Sex	1905			
Male	682 (35.8%)			
Female	1223 (64.2%)			
Total Cholesterol (mg/dL)	1530	197.7	194.0	80.0, 418.0
HDL-C (mg/dL)	1529	54.6	52.0	22.0, 171.0
LDL-C (mg/dL)	1479	119.2	116.8	25.6, 290.4
Triglycerides (mg/dL)	1530	122.2	105.0	23.0, 3170.0

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Table 2

## Regions Suggested by Admixture Mapping

Phenotype	Chromosome and Region (Mb)*	Peak SNP in the region	$-\log_{10}(\text{p-value})$
Total Cholesterol	Chromosome 19: 4.9 — 40.1	rs901792	3.06
HDL-C	Chromosome 8: 16.8 — 27.4	rs13438843	3.05
LDL-C	Chromosome 7: 16.8 — 23.4	rs7793253	3.21
Triglycerides	Chromosome 14: 78.3 — 95.6	rs3825663	3.26
	Chromosome 19: 1.6 — 8.1	rs8110664	3.96

Mb - Mega base pairs

\* Region is the 1 unit drop of  $-\log_{10}(\text{p-value})$  of the peak SNP in the region.

Table 3

## Significant Fine-Mapping Results

Phenotype (Chr <sup>§</sup> )	# SNPs tested	Bonferroni-Corrected Significance Level	Significant SNPs [call rate]	Beta	SE	Wald p-value	Effect Allele Frequency in CEU <sup>#</sup> /YRI <sup>#</sup>	SNP-Specific Heritability	CARE Replication Beta (p-value)
HDL (8)	10,995	$4.55 \times 10^{-6}$	rs10096633 [99.97%]	2.10	0.41	$4.17 \times 10^{-7}$	T 0.142/ 0.493	0.017	0.1008 ( $1.48 \times 10^{-9}$ )
			rs13702 [99.92%]	-1.89	0.41	$3.44 \times 10^{-6}$	T 0.712/ 0.418	0.014	-0.0981 ( $2.49 \times 10^{-9}$ )
LDL (7)	6,964	$7.18 \times 10^{-6}$	rs12534314 <sup>‡</sup> [99.92%]	-8.50	1.92	$9.29 \times 10^{-6}$	T 0.185/ 0.032	0.013	0.0031 (0.9183)
			rs6966083 [100%]	-18.27	4.14	$1.02 \times 10^{-5}$	T 0.509/ 0.194	0.010	0.183 (0.01181)
			rs12531660 <sup>‡</sup> [99.92%]	-8.22	1.93	$2.13 \times 10^{-5}$	G 0.172/ 0.025	0.014	NA**
			rs10486301 [100%]	-8.34	2.14	$9.37 \times 10^{-5}$	C 0.231/ 0.008	0.018	-0.0092 (0.8083)
Triglycerides (14)	15,328	$3.26 \times 10^{-6}$	rs10483943 <sup>‡</sup> [100%]	36.95	7.24	$3.35 \times 10^{-7}$	G 0.185/ 0.008	0.012	NA**
			rs759512 <sup>‡</sup> [100%]	35.97	7.28	$7.74 \times 10^{-7}$	T 0.194/ 0.008	0.011	NA**
			rs757645 <sup>‡</sup> [100%]	33.05	6.94	$1.92 \times 10^{-6}$	A 0.169/ 0.017	0.009	NA**
			rs10130530 [100%]	53.28	11.24	$2.13 \times 10^{-6}$	A 0.023/ 0.008	0.024	NA**
			rs11620666 [100%]	23.85	5.11	$3.08 \times 10^{-6}$	T 0.418/ 0.008	0.005	NA**

<sup>‡</sup> In linkage disequilibrium ( $D' = 1.00$ ,  $r^2 = 1.00$ ) on chromosome 7.

<sup>‡</sup> In linkage disequilibrium ( $D' = 1.00$ ,  $r^2 = 1.00$ ) on chromosome 14.

<sup>§</sup> Chr, chromosome number

<sup>#</sup> CEU, Utah residents with Northern and Western European ancestry from the CEPH collection from the International HapMap Project

<sup>#</sup> YRI Yoruba in Ibadan, Nigeria from the International HapMap Project

\*\* NA, not available